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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/957,031	09/21/2001	David Margolis	A8163	6530

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EXAMINER

SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 11/05/2002

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/957,031		Applicant(s) MARGOLIS ET AL.	
	Examiner Daniel M Sullivan		Art Unit 1636	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 06 September 2002.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 89-190 is/are pending in the application.

4a) Of the above claim(s) 101-108, 129-136 and 161-168 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 89-100, 109-127, 137, 140-145, 148-160 and 169-190 is/are rejected.

7) ☒ Claim(s) 128, 138, 139 and 147 is/are objected to.

8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on 21 September 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>2</u> .	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) 6) <input type="checkbox"/> Other: _____
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DETAILED ACTION

This is a First Office Action on the Merits of the pending Application filed September 21, 2001, which is a Divisional Application of copending Application 09/210,578 filed December 14, 1998, now U.S. Patent No. 6,340,591. This Office Action is a reply to the Response to Restriction and Election of Species Requirement filed September 6, 2002 (Paper No. 7) in response to the Restriction Requirement mailed August 6, 2002 (Paper No. 6). The preliminary Amendment filed September 21, 2001 (Paper No. 3) has been entered. Claims 1-88 were cancelled and claims 89-190 were added in Paper No. 3.

Election/Restrictions

Applicant's election without traverse of Group I, claims 89-100, 109-128, 137-160 and 169-190, in Paper No. 6 is acknowledged. In response to the requirement for election of a species for examination of claims 179-181 and 188, Applicant has elected the p47 phox gene.

Claims 101-108, 129-136 and 161-168 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 89-100, 109-116, 140, 148-160 and 169-190 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* applications, does not reasonably provide enablement for *in vivo* use. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The invention claims a composition comprising a vector delivery structure comprising a cochleate vector and a pharmaceutically acceptable carrier and methods of using said cochleate vector comprising proteins (that facilitate integration into the genome) and a polynucleotide sequence (that enables binding to the genome) for the delivery of a nucleotide into the genome for integration. Even though the invention claims compositions comprising the cochleate the vector and the use of the cochleate vector or composition comprising the cochleate vector in gene therapy applications, the specification does not teach one skilled in the art to which it pertains how to use this invention. The claims are enabled for *in vitro* applications but not for *in vivo* or *ex vivo* applications.

The state of the art in gene therapy is still in its infancy and is highly unpredictable. "Clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol" (see Orkin et al. Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, distributed by the National Institutes of Health, Bethesda, MD or www.nih.gov, page 1, IDS #12).

Gene therapy aims to alleviate or cure diseases by altering the genetic makeup of the individual. The first clinical trials for genetic therapy were conducted in 1990. However, there is still no single outcome to point to as a success story after hundreds of clinical trials have been

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performed worldwide on thousands of individuals. (See Verma, M. et al., Gene Therapy-promises, problems and prospects, Nature Vol. 389 page 239, paragraph # 2, IDS #11). The major problems that have been encountered are (1) the delivery of the altered genes, and (2) the inability to obtain a sustained expression of the desired protein in a specified location. (See Verma, M. et al., Gene Therapy-promises, problems and prospects, Nature Vol. 389 page 239, paragraph # 5).

Being a new field the amount of direction or guidance necessary in the specification has to be very detailed in order to provide enablement. In this case, the state of the prior art does not teach one skilled in the art how to transfer a gene and induce a therapeutic response in vivo. The specification teaches how to transform cells in vitro but the scope of the claims encompass in vivo methods of use. Hence the specification lacks detailed methods as to how to use the said vector, including specific dosages for specific therapies, in order for this vector to be used in in-vivo applications as claimed by the inventions. This is made clear by the MPEP 608.01(p) where it states: "If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied...".

The specification describes the preparation of a cochleate vector which functions as an integrative lipid DNA vector targeted to human CD34⁺ progenitor cell targets in vitro, but does not teach how this is to be used for therapy. Details on the formulation protocol for the said integrative cochleate vectors, and specific formulations utilized in gene transfer experiments have been documented in the specification. Gene transfer experiments have been performed

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using CD34⁺ cells from neonatal cord blood or from adult volunteers under a University of Maryland human use protocol.

Experiments conducted by the applicants demonstrated that a gene flanked by the MV ITRs and formulated with Rep 68 and Rep 78 proteins and cochleates transferred a marker gene which was expressed over 10-14 days in culture in hematopoietic colony forming cells. The experiments also demonstrated that the ITR and Rep proteins improved the efficiency of the process. According to their results, this is an improvement over standard retroviral vector gene transfer. Also shown were experiments using retroviral gene transfer protocols employing cytokine stimulation additionally, resulting in more efficient gene transfer. However, these in vitro data cannot be extrapolated to the in vivo environment and to a therapeutic application.

For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (IDS #13) explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. [See Eck et al., bridging pages 81-82.]

Examples 4 and 5 in the specification are not directed to any specific experiments performed by the applicant. Prophetic statements about the possibilities envisioned by the

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applicant for uses of the integrative cochleate DNA vector are stated. There are no experiments to support the treatment of genetically abnormal hematopoietic progenitor cells, or the correction or modulation of metabolic pathways, or the treatment of cancer cells with therapeutic genes.

In view of this, it would prove an arduous task for one skilled in the art to be able to practice the claimed invention of gene therapy. Hence, since one skilled in the art cannot readily anticipate the results predicted within the subject matter to which the claimed invention pertains, then there is a lack of predictability in the art. In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the amount of guidance set forth, the breadth of the claims, and the lack of working examples, one of skill in the art could not make and use the invention without undue experimentation. The composition of claims 89-116 are therefore enabled only to the extent that they are directed to a composition for transforming a host cell for *in vitro* applications. Claims 149-190, which are drawn to methods of *ex vivo* gene therapy and compositions expressly for the purpose of treatment by gene therapy are not enabled over any scope.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 89-100 and 109-116 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,340,591. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant Application are identical in scope to the patented claims except that the instant claims are further limited to a composition comprising a pharmaceutically acceptable carrier. The added limitation would be obvious to one of ordinary skill in the art in view of the explicit teaching of the specification that the claimed compositions may comprise pharmaceutically effective carriers (6,340,591 Patent, column 8, lines 14-15).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Note: The following rejection applies to the extent that the prior art discloses the same compositions and/or method embraced by the instant invention. The prior art rejection is not to be construed as an indication that the claimed or anticipated methods are *enabled* for the wide breadth of subject matter potentially embraced by the claims. The compositions and/or methods disclosed in the prior art are essentially enabled to the same extent as the instant specification, since there is no significant difference in the level of guidance presented in either case.

Claims 89-99, 109, 111-115, 117-127, 137, 140-145, 148-159, 169, 172-176, 182-184 and 189 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiener *et al.* (U.S. Patent 6,342,390, filed November 23, 1994) in view of Mannino and Gould-Fogerite (1996; WO 96/25942).

Claim 89, and claims 90-99, 109 and 184 depending therefrom, are directed to a composition comprising: a) a vector delivery structure comprising: 1) a cochleate comprising a lipid bilayer element and cations; 2) one or more proteins that facilitate the integration of one or

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more nucleotide sequences, that express a molecule, into the genome of a host cell; and 3) a polynucleotide comprising one or more DNA sequences recognized and bound by the one or more proteins and one or more oligonucleotides or polynucleotides, each containing said one or more nucleotide sequences; and b) a pharmaceutically acceptable carrier.

Wiener *et al.* teach a vector delivery structure comprising one or more proteins that facilitate the integration of one or more nucleotide sequences, which express a molecule, into the genome of a host cell and a polynucleotide comprising one or more DNA sequences recognized and bound by the one or more proteins and one or more oligonucleotides or polynucleotides, each containing said one or more nucleotide sequences (see especially the first paragraph in column 2). Wiener *et al.* further teach that the above composition can be comprised within an encapsulating medium such as a liposome (see especially the third full paragraph of column 4). Wiener *et al.* does not explicitly teach a pharmaceutically acceptable carrier; however, Weiner *et al.* does contemplate intravenous administration of the composition (see especially Example 4, bridging columns 11 and 12), which would require the use of a pharmaceutically acceptable carrier.

Weiner *et al.* does not teach a vector delivery structure comprising a cochleate or limitations relevant only to a cochleate structure.

Claim 111, and claims 112-115 and 184 depending therefrom, are directed to a composition comprising: a) a vector delivery structure for delivering to the interior of a host cell one or more therapeutic nucleotide sequences, that express a molecule, and one or more proteins that bind to DNA for facilitating the integration of the one or more nucleotide sequences into the genome of the host cell, the vector delivery structure comprising: 1) a cochleate comprising a

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lipid bilayer element and cations; 2) one or more proteins that facilitate the integration of one or more nucleotide sequences, that express a molecule, into the genome of a host cell; and 3) a polynucleotide comprising one or more DNA sequences recognized and bound by the one or more proteins and one or more oligonucleotides or polynucleotides, each containing said one or more nucleotide sequences; and b) a pharmaceutically acceptable carrier.

Weiner *et al.* teach the vector delivery structure described above further comprising various therapeutic nucleotide sequences (see especially the paragraph bridging columns 3 and 4).

As above, Weiner *et al.* does not teach a vector delivery structure comprising a cochleate or limitations relevant only to a cochleate structure.

Claim 117, and claims 118-127, 137, 140 and 189 depending therefrom, are directed to a method for transforming a host cell in vitro with one or more nucleotide sequences, that express a molecule, the method comprising transfecting a host cell in vitro with a vector delivery structure comprising: a) a cochleate comprising a lipid bilayer element and cations; b) one or more proteins that facilitate the integration of said one or more nucleotide sequences into the genome of said host cell; and c) a polynucleotide comprising one or more DNA sequences recognized and bound by the one or more proteins and one or more oligonucleotides or polynucleotides, each containing said one or more nucleotide sequences.

Weiner *et al.* teach a method for transforming a host cell in vitro with one or more nucleotide sequences, that express a molecule, the method comprising transfecting a host cell in vitro with the vector delivery structure described herein above (see especially the first full paragraph in column 6).



As above, Weiner *et al.* does not teach a vector delivery structure comprising a cochleate or limitations relevant only to a cochleate structure.

Claim 141, and claims 142-145 and 148 depending therefrom, are directed to a method for transforming a host cell in vitro with one or more nucleotide sequences, that express a molecule, the method comprising transfecting said host cell in vitro with a vector delivery structure for delivering to the interior of the host cell said one or more nucleotide sequences and one or more binding proteins for facilitating the integration of the one or more nucleotide sequences into the genome of the host cell, the vector delivery structure comprising: a) a cochleate comprising a lipid bilayer element, wherein the layers of the lipid bilayer element are bound together by a divalent calcium cation; b) a DNA binding protein of adeno-associated virus type II comprising a Rep 68 protein or a Rep 78 protein; and c) a polynucleotide comprising one or more inverted terminal repeat regions.

Weiner *et al.* teach a method for transforming a host cell in vitro with one or more nucleotide sequences, that express a molecule, the method comprising transfecting a host cell in vitro with the vector delivery structure described herein above and further comprising the Rep 68 or Rep 78 DNA binding proteins and one or more inverted terminal repeat regions (see especially the second and third full paragraphs in column 2).

As above, Weiner *et al.* does not teach a vector delivery structure comprising a cochleate or limitations relevant only to a cochleate structure.

Claim 149, and claims 150-159 and 169 depending therefrom, are directed to a method for ex vivo treatment of a subject in need thereof, comprising: a) transforming a host cell in vitro with one or more nucleotide sequences, that express a molecule, with a vector delivery structure

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comprising: 1) a cochleate comprising a lipid bilayer element and cations; 2) one or more proteins that facilitate the integration of one or more nucleotide sequences, that express a molecule, into the genome of a host cell; and 3) a polynucleotide comprising one or more DNA sequences recognized and bound by the one or more proteins and one or more oligonucleotides or polynucleotides, each containing said one or more nucleotide sequences, and b) administering said in vitro transformed host cell to said subject.

Weiner *et al.* contemplate using the vector delivery structure described herein above as a vehicle for *ex vivo* treatment of Hemophilia B (see especially example 2 bridging columns 10 and 11).

As above, Weiner *et al.* does not teach a vector delivery structure comprising a cochleate or limitations relevant only to a cochleate structure.

Claim 172, and claims 173-176 depending therefrom, are directed to a method for *ex vivo* treatment of a subject in need thereof comprising: a) transforming a host cell in vitro with one or more nucleotide sequences, that express a molecule, comprising a vector delivery structure for delivering to (the interior of the host cell said one or more nucleotide sequences and one or more binding proteins for facilitating the integration of the one or more nucleotide sequences into the genome of the host cell, the vector delivery structure comprising: 1) a cochleate comprising a lipid bilayer element, wherein the layers of the lipid bilayer element are bound together by a divalent calcium cation; 2) a DNA binding protein of adeno-associated virus type II comprising a Rep 68 protein or a Rep 78 protein; and 3) a polynucleotide comprising one or more inverted terminal repeat regions of the adeno-associated virus and one or more oligonucleotides or

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polynucleotides, each containing said one or more nucleotide sequences, and b) administering said in vitro transformed host cell to said subject.

Weiner *et al.* teach that the vector delivery structure used in the method of *ex vivo* treatment of Hemophilia B should comprise the Rep 68 or Rep 78 DNA binding proteins and one or more inverted terminal repeat regions (see especially example 2 bridging columns 10 and 11).

As above, Weiner *et al.* does not teach a vector delivery structure comprising a cochleate or limitations relevant only to a cochleate structure.

The base claims recited above are variously further limited by the dependent claims to compositions or methods wherein: the polynucleotide is selected from the group consisting of a plasmid or nucleic acid construct; the vector delivery structure comprises a polynucleotide that expresses one or more proteins that facilitate integration; the cations are divalent cations; the cations are calcium; the proteins that facilitate the integration of one or more nucleotide sequences into the genome of a host cell are one or more binding proteins that have a DNA binding motif; the one or more binding proteins are from adeno-associated virus type II; the one or more binding proteins are Rep 68 or Rep 78; the DNA sequences recognized and bound by the proteins are the inverted terminal repeat regions of adeno-associated virus; the oligonucleotides or polynucleotides comprise a length of DNA that is flanked at each end by at least one of the inverted terminal repeat regions; the host cell is a human cell; and the one or more nucleotide sequences that express a molecule is a normal gene for a clotting factor.

Weiner *et al.* teaches: a polynucleotide which is a plasmid or nucleic acid construct and further comprises a polynucleotide that expresses one or more proteins that facilitate integration (see especially the second full paragraph of column 3); the one or more binding proteins are Rep

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68 or Rep 78 and a polynucleotide flanked by AAV inverted terminal repeat regions (as cited herein above); a host cell that is a human cell (see especially the first full paragraph of column 6); and a nucleotide sequence that expresses a normal clotting factor (see especially the paragraph bridging columns 3 and 4).

Therefore, Weiner *et al.* teach all of the limitations of the claims except for a vector delivery structure comprising a cochleate or limitations relevant only to a cochleate structure.

Mannino and Gould-Fogerite teaches a cochleate structure comprising a lipid bilayer wherein the layers of the lipid bilayer element are bound together by a divalent cations, and the use of said cochleate structure to deliver polynucleotides into cells (see especially the paragraph bridging pages 2 and 3, and page 3, beginning line 17 and continuing through the second line on page 4). Mannino and Gould-Fogerite further teach that the divalent cations can be calcium cations (see especially page 14, line 5). Again, the limitation of the cochleate structure comprised within a pharmaceutically acceptable carrier is indicated by the use of the cochleate structures of Mannino and Gould-Fogerite to transfer a gene *in vivo* (see especially Example 4, beginning on page 27).

These teachings demonstrate that compositions comprising one or more proteins that facilitate the integration of one or more nucleotide sequences, which express a molecule, into the genome of a host cell and a polynucleotide comprising one or more DNA sequences recognized and bound by the one or more proteins and one or more oligonucleotides or polynucleotides, each containing said one or more nucleotide sequences were known to skilled practitioners of the art at the time the Weiner *et al.* patent was filed. In addition, as evidenced by Mannino and Gould-Fogerite, at the time that the instant Application was filed the use of cochleate structures

to transfer DNA and proteins into cells was also known in the art. Furthermore, both of the cited references contemplated using their respective compositions for gene therapy methods.

It would have been obvious to one of ordinary skill in the art at the time the instant Application was filed to modify the teachings of Weiner *et al.* to include the cochleate structure taught by Mannino and Gould-Fogerite to produce the composition claimed in the instant Application and to use the composition according to the claimed methods. Mannino and Gould-Fogerite teach many advantages of cochleate structures as vehicles for delivery of biologically active molecules, which provides strong motivation to combine the teachings (see especially beginning on page 4, line 13, and continued through line 18 on page 5).

In the absence of evidence to the contrary, the skilled artisan would have a reasonable expectation of success in combining these teachings in view of the versatility of cochleates as vehicles for transfer of molecules into cells taught by Mannino and Gould-Fogerite (throughout).

Allowable Subject Matter

Claims 128, 138, 139, 146 and 147 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claims 89-100, 109-127, 137, 140-145, 148-160 and 169-190 are rejected.

Claims 128, 138, 139, 146 and 147 are objected to.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448.

The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
October 31, 2002



**JAMES KETTER
PRIMARY EXAMINER**